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Review Article

Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon

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Summary

Coumarin oral anticoagulant drugs have proven to be effective for the prevention of thromboembolic events. World-wide, warfarin is the most prescribed drug. In Europe, acenocoumarol and phenprocoumon are also administered. Yet it has been proven that variant alleles of the VKORC1 and CYP2C9 genotypes influence the pharmacokinetics and pharmacodynamics of these drugs. The combination of these two variant genotypes is a major cause of the inter-individual differences in coumarin anticoagulant drug dosage. Individuals who test positive for both variant genotypes are at increased risk of major bleeding. The impact of the CYP2C9 and VKORC1 genotype is most significant during the initial period of coumarin anticoagulant therapy. The effect of VKORC1 allelic variants is relatively similar for all three VKAs. The CYP2C9 polymorphism is associated with delayed stabilisation for coumarin anticoagulants. The effects of CYP2C9 polymorphisms on the pharmacokinetics and anticoagulant response are least pronounced in the case of phenprocoumon. In the long term, patients using phenprocoumon have more often international normalised ratio (INR) values in the therapeutic range, requiring fewer monitoring visits. This leads us to conclude that in the absence of pharmacogenetic testing, phenprocoumon seems preferable for use in long-term therapeutic anticoagulation. Pharmacogenetic testing before initiating coumarin oral anticoagulants may add to the safety of all coumarin anticoagulants especially in the elderly receiving multiple drugs.

Keywords

Clinical trials, oral anticoagulants, pharamacogenetics, pharmacodynamics

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Introduction

Coumarin anticoagulants, also called vitamin K antagonists (VKAs), are effective in the prevention of venous and arterial thromboembolism (1). VKAs suppress the regeneration of the reduced form of vitamin K by inhibiting vitamin K epoxide reductase. The vitamin K cycle regenerates reduced vitamin K1 from its epoxide. Reduced vitamin K is a cofactor for post-translational gamma-carboxylation of glutamic acid residues on several proteins for normal haemostasis. This results in negatively charged gamma-carboxyglutamates on factors II, VII, IX, and X, which bind to calcium cations and then to platelet phospholipid membranes. Gamma-carboxylation is also required for the development of other tissues. VKAs also inhibit the gamma-carboxylation of anticoagulant proteins C, S, Z, and osteocalcin. VKAs inhibition of clotting factor activity is their main pharmacologic effect. This is responsible for VKAs ability to inhibit clot formation.

The major side effect of VKAs is major bleeding, with reported incidences of 1.5 to 5.0 per 100 patient-years (2, 3). The incidence of both bleeding and thromboembolic events increases sharply with advanced age. The risk of over- and under-coagulation in patients taking VKAs is associated with drug-VKAs interactions, food-VKAs interactions, and disease-VKAs interactions. Alcohol consumption, liver disease, and other unknown factors also influence optimal daily dosages. Other inter-individual variations that affect predicting optimal daily dosages include pharmacogenetic predisposition, age and patient obesity, which corresponds to the amount of coumarin anticoagulants required for initiation of therapy (4–6). This explains why oral anticoagulants have a small therapeutic window, and the stability of anticoagulant therapy can be easily disturbed.

Both safety (primarily risk of bleeding) and effectiveness of VKAs therapy relates to blood international normalised ratio (INR) values (7). Monitoring of INR and dose adjustments of coumarin anticoagulants are frequently required. Futhermore,

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pharmacogenetics, the field of research describing the influence of variations of DNA characteristics on drug response, plays an important role in the safety and effectiveness of VKAs.

Warfarin is the VKAs drug of choice in most countries. Yet acenocoumarol and phenprocoumon are used in many European countries, including The Netherlands and Germany. Several reviews and research papers on the pharmacogenetic influences of warfarin are available (8, 9). Comparatively systematic information on the pharmacogenetic influences of acenocoumarol and phenprocoumon is scarce. In this review, we focus on the pharmacogenetics of phenprocoumon and acenocoumarol, comparing these drugs with the pharmacogenetics of warfarin. We also explored these drugs' relevance to therapeutic choices.

We performed the literature search in EMBASE and Medline (PUBMED) from 1995 to June 2008. We included studies with original data on pharmacogenetics of phenprocoumon and acenocoumarol. Data from warfarin reviews and additional relevant papers not included in the cited reviews were also included. Search words and terms included: pharmacogenetics and/or pharmacogenomics; acenocoumarol; phenprocoumon; CYP2C9 and/or genotype and /or polymorphism; VKORC1; warfarin and review; and coumarin anticoagulants.

Cytochrome P450 2C9 and VKORC1 and other genetic variants

Cytochrome P450 (CYP) is a group of hepatic microsomal enzymes that act as monooxygenases of endobiotics (steroid hormones, fatty acids derivates, and vitamins) and xenobiotics (drugs, pollutants, and carcinogens). The abbreviation CYP, followed by a number, a capital letter and another number (e.g. CYP2D6, CYP3A4, CYP2C9), designates an individual enzyme from this group of monooxygenases. Cytochromes transform lipophilic drugs into more hydrophilic metabolites which facilitates further elimination and renal excretion.

The gene *CYP2C9* encodes the enzyme CYP2C9, of which about 30 variant alleles have been described. The most frequently occurring variant alleles in Caucasians are *CYP2C9*2* (CGT>TGT in exon 3) and *CYP2C9*3* (ATT>CTT in exon 7) (10).

These factors lead CYP2C9 to play a role in the metabolism of:

- Coumarin anticoagulant drugs (warfarin, acenocoumarol, phenprocoumon)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. diclofenac, ibuprofen, lornoxicam, celecoxib, flurbiprofen, naproxen)
- Sulfonylureas (e.g. tolbutamide, glipizide)
- Phenytoin

Inhibitors of CYP2C9 include some SSRI type antidepressants (e.g. fluoxetine, fluvoxamine), amiodarone, benzbromarone, cotrimoxazol, cimetidine and antimycotic drugs (e.g. fluconazole, miconazole, voriconazole). Inducers of CYP2C9 include rifampicin and carbamazepin.

The gene *VKORC1* encodes vitamin K-epoxide reductase (VKORC1), of which several variant alleles have been described. Coumarin anticoagulant derivatives targets VKORC1. This complex recycles reduced vitamin K, which is essential for the post-translational gamma-carboxylation of vitamin K–dependent clotting factors II (prothrombin), VII, IX, and X, and of proteins C, S and Z.

The impact of other enzymes polymorphisms, like GGCX (gamma-glutamyl carboxylase), on coumarin anticoagulant dose finding has been examined, but there are no significant results.

Warfarin

Warfarin is a racemate, with S-warfarin being three times as potent as R-warfarin. The S-enantiomer in warfarin is predominantly responsible for the anticoagulant effect. When administered orally, warfarin is completely absorbed and 99% is bound to albumin in the plasma. The liver absorbs the free warfarin where it exerts its anticoagulant effect and is metabolized by several CYP-enzymes.

Yet from a clinical standpoint, R-warfarin is the most active anticoagulant. This is because CYP2C9 metabolises S-warfarin in the first-pass-effect very efficiently. CYP2C9 converts the S-enantiomer to 6- and 7-hydroxy-warfarin, which is eventually excreted in the bile. In comparison, CYP1A1, CYP1A2, and CYP3A4 metabolize R-enantiomer into an inactive alcohol-metabolite excreted in the urine.

Patients with either a CYP2C9*2 or CYP2C9*3 polymorphism have impaired metabolism of the more active enantiomer S-warfarin when compared to patients who are homozygous for the wild-type allele CYP2C9*1 (11). The unbound *S*-warfarin clearance is about two- to three-fold lower in heterozygous carriers of the *CYP2C9*3* allele and about 10-fold lower in homozygous carriers (12).

In vivo, these two CYP2C9 SNPs have been associated with increased responsiveness to warfarin (13). Aithal et al. (14) compared controls requiring typical warfarin doses to patients whose therapeutic warfarin dose was 10.5 mg/week or less. They found that patients requiring low doses of warfarin were more prone to a supratherapeutic INR at the time of warfarin induction; were almost four times more prone to bleed; and were six times more likely to have the CYP2C9*2 or CYP2C9*3 SNPs. Others found that CYP2C9*3 decreased the selectivity of CYP2C9 for S-warfarin and that residue 359, the mutated amino acid, was a component of the warfarin-binding site.

Patients with one or two of these SNPs have reduced warfarin requirements and an elevated risk of an adverse event by initial warfarin therapy. The CYP2C9 SNPs are associated with a two- to three-fold increased risk of bleeding during warfarin induction (15). This observation suggests that pharmacogenetics-based warfarin therapy will mainly affect the initial warfarin dosage(s). However, because a CYP2C9 polymorphism is also associated with a decreased chance to achieve stable anticoagulation (16), it is possible that genotype-steered dosing can also play a role during later stages of warfarin therapy.

Recently CYP4F2 genetic variants were associated with a clinically relevant effect on warfarin requirement in the Caucasian population (17). Data from other ethnic groups and the role CYP4F2 in acenocoumarol and phenprocoumon dose requirement are lacking.

Several genetic variations of the VKORC1 gene have been found to influence sensitivity to warfarin (18, 19). Four different heterozygous mutations in the VKORC1 gene were found in individuals with warfarin resistance. Rieder et al. (18) investigated the genetic basis of the broad variation among patients in response to warfarin therapy. They determined the VKORC1 haplotype frequencies in African-American, European-American and Asian-American populations, and they found VKORC1 mRNA expression in human liver samples. They found 28 VKORC1 SNPs in the primary population. Rieder et al. identified 10 common (>5%) noncoding VKORC1 single-nucleotide polymorphisms (SNPs) and inferred five major haplotypes, from which a low-dose haplotype group (A) and a high-dose haplotype group (B) were derived.

Initial variability in the INR response is more strongly associated with VKORC1 than with CYP2C9 (20). The mean maintenance dosages of warfarin differs significantly among the three haplotype group combinations, at approximately 2.7 mg/day for A/A, 4.9 mg/day for A/B, and 6.2 mg/day for B/B. VKORC1 haplotype groups A and B explains approximately 25% of the variance in warfarin dose. Moreover, one single nucleotide polymorphism, such as C1173T in intron 1, appears to be as informative about coumarin anticoagulant sensitivity as all the five major haplotypes, which represents 96% to 99% of the total haplotypes. Asian-Americans have a higher proportion of group A haplotypes, and African-Americans have a higher proportion of group B haplotypes. Wadelius et al. (21) finds that VKORC1 SNPs covaried significantly with warfarin dose, which explains 30% of dose variations (22). Cytochrome P450 2C9 (CYP2C9) explains 12% of variance in warfarin dose (23). The VKORC1 C1173 polymorphism is in strong disequilibrium with VKORC1 promotor 1639. In Europeans, guanine (G) is expressed. In some other ethnic groups, adenine(A) is more common. A heterozygous or homozygous adenine (A) significantly reduces VKOR expression compared with G / G. The VKORC1 variation p.Trp59Arg (24) and Asp36Tyr (25) have been described to explain coumarin resistance.

Incorrect dosage, especially during the initial phase of treatment, carries a high risk for either severe bleeding or failure to prevent thromboembolism. Genotype-based dose predictions may enable personalized drug treatment from the start of warfarin therapy (26).

Acenocoumarol

Like S-warfarin, S-acenocoumarol is more potent than R-acenocoumarol and is metabolized by CYP2C9 (27–30). CYP1A2, 3A4, 2C9 and 2C19 metabolize R-acenocoumarol. An important pharmacokinetic difference between warfarin and acenocoumarol is that S- and R-warfarin have half-lives of approximately 32 and 43 hours, while S- and R-acenocoumarol have half lives of 2 and 8 hours. As a result of slower elimination of the *S*-enantiomer, R-acenocoumarol is largely responsible for the overall anticoagulant response. Furthermore, R-acenocoumarol is clini-

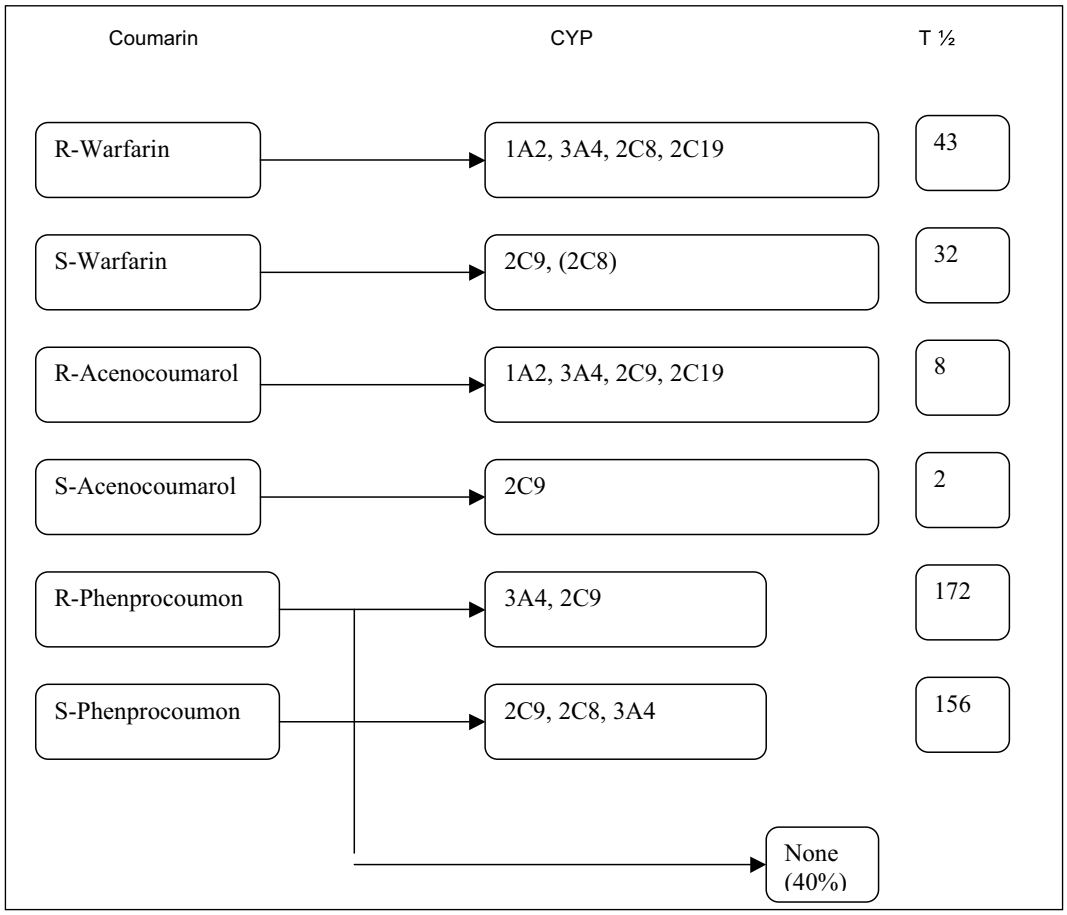

Figure 1: The influence of CYP isoenzymes on coumarin anticoagulant hydroxylation.

cally the more important enantiomer because of the very short half-life of S-acenocoumarol (31).

Patients with a CYP2C9 variant allele have a higher risk of early acenocoumarol overanticoagulation (32, 33). Patients with the CYP2C9*3, but not the CYP2C9*2 variant, are known to require a lower maintenance dose of racemic acenocoumarol (34–37). The S-acenocoumarol clearance in a heterozygous carrier of the CYP2C9*3 allele is more than 15-fold lower than in wild-type subjects. This difference between CYP2C9*2 and *3 discerns acenocoumarol from warfarin.The S-acenocoumarol plasma half-life is prolonged in the CYP2C9*1/*3 genotypes.

The effect is that S-acenocoumarol pharmacokinetics is dependent on the CYP2C9 genotype. Specifically, the presence of the CYP2C9*3 allele impairs oral clearance of the coumarin anticoagulants. The time needed to achieve stability is mainly associated with the CYP2C9 genotype.

The genotype VKORC1 modifies the effect of the CYP2C9 genotype on the anticoagulation status (38). In several studies, the VKORC1 genotype, rather than by the CYP2C9 genotype, explains a larger part of the dose requirement. Severe, over anticoagulation is mostly associated with the combination of variant alleles of CYP2C9 and VKORC1 (39–41).

Phenprocoumon

Phenprocoumon seems preferable in poor metabolisers of coumarin anticoagulants (42). Phenprocoumon has a long half-life: it is approximately 172 hours for the more potent S-phenprocoumon enantiomer, and approximately 156 hours for R-phenprocoumon. The *S*-enantiomer is predominantly responsible for the anticoagulant effect in phenprocoumon. The S-7-hydroxylation is the most important metabolising factor (43, 44). Yet the *2 and *3 allele significantly compromises the S-7-hydroxylation in a gene-dose-dependent manner. Phenprocoumon metabolism appears to be less influenced by the 2C9 genotypes when compared with other coumarin anticoagulants (45, 46). S- and R- phenprocoumon are predominantly metabolised by CYP2C9 and 3A4 (Fig. 1).

The significant role of the non-polymorphic 3A4 in phenprocoumon metabolism makes it a possibly safer drug to use over other coumarin anticoagulants. The oral clearance of S-acenocoumarol is more than 15-fold lower in a carrier of the heterozygous *3 genotype compared with the *1 *1 genotype. The oral clearance of S-phenprocoumon is only marginally reduced in variant allele carriers (47). The clearance of R-phenprocoumon is essentially unchanged. About 40% of an oral dose of phenprocoumon is excreted unchanged (48, 49), whereas warfarin and acenocoumarol are almost completely metabolised (Table 1) (50). Phenprocoumon therefore seems preferable in poor metabolisers of coumarin anticoagulants.

Finally, like S-warfarin and S-acenocoumarol, both S- and R-phenprocoumon inhibit vitamin K epoxide reductase (the S-enantiomer being 2–5 times as potent as the R-enantiomer).

The effects of the CYP2C9 polymorphisms on the pharmacokinetics and anticoagulant response are least pronounced for phenprocoumon, yet the VKORC1 genotype can modify the effect of the CYP2C9 genotype on phenprocoumon dose requirements. Greater variability in dose requirement is observed by the VKORC1 genotype than by the CYP2C9 genotype. Schalekamp et al. showed that in patients without a VKORC1 variant allele, carriers of a CYP2C9 variant need dosages that are nearly 30% lower than those for CYP2C9*1/*1 patients (51). In patients with a VKORC1 variant allele, differences between carriers of a CYP2C9 variant and CYP2C9*1/*1 are statistically insignificant, suggesting that differences between CYP2C9 genotypes mainly apply to patients without a VKORC1 variant allele. Carriers with a combination of CYP2C9 variant and VKORC1 variant alleles show a significant increase in the risk of severe overanticoagulation, whereas delayed stabilization is mainly associated with the CYP2C9 genotype. Carriers of the *3 allele have a higher risk of bleeding (52). From a clinical perspective, the bleeding risk of patients using phenprocoumon should be taken into consideration (53).

Patients using phenprocoumon have more stable INR values than patients on acenocoumarol and require fewer monitoring visits (54, 55). Because of the long half-life time, overanticoagulated patients using phenprocoumon are at greater risk of major bleedings due to the prolonged period of overanticoagulation.

Coumarin anticoagulants and NSAIDs drug-drug interactions

CYP2C9 metabolises several drugs (see above), especially some NSAIDs, making a pharmacokinetic interaction with the coumarin anticoagulants conceivable (56–58). The effects of NSAIDs are well documented. NSAIDs (excluding cyclooxygenase [COX]2-selective NSAIDs) inhibit platelet aggregation which increases the risk of bleeding (59). This pharmacodynamic interaction is not reflected by a change in the prothrombin time as

Table 1: The impact of pharmacogenetics on the different coumarin drugs. T ½ is the half-life time of a coumarin in the blood. The dose variance is the impact of the genotype on the coumarin dose required to get INR values within target range. The administration of NSAIDs can delay the metabolism of some coumarins.

	Dose variance (%)			NSAID
	T ½ (hours)	VKORC1	CYP2C9	Delayed metabolism
Warfarin	32–43	25 (14–36)	13 (4–21)	1.32 fold
Acenocoumarol	2–8	29 (21–36)	10 (5–14)	1.28 fold
Phenprocoumon	156–178	29	7	1.11 fold

What is known about this topic?
– Coumarin anticoagulants are metabolized predominantly by CYP2C9. Their target on the enzyme vitamin K epoxidase is VKORC1.
– CYP2C9 and VKORC1 genetic variants are associated with variability in coumarin anticoagulant dose requirement, overanticoagulation, stabilization and bleeding risk.

What does this paper add?
– In this paper a comparison is made between the role of CYP2C9 and VKORC1 genetic variants for the coumarin anticoagulants warfarin, acenocoumarol and phenprocoumon.
– We conclude that the impact of genetic variants of CYP2C9 and VKORC1 on warfarin, acenocoumarol and phenprocoumon is quite different.

measured by the INR. Kohl et al. introduced a model to approach the interaction of NSAIDs with coumarin anticoagulants based on CYP2C9 and compared it with studies *in vivo*. They found an increase in plasma concentrations of coumarin anticoagulants: 1.32 fold for racemic warfarin; 1.28 fold for racemic acenocoumarol; 1.11 fold for racemic phenprocoumon. For S-warfarin the increase is 1.58-fold; for S-phenprocoumon it was 1.13 fold.

In patients treated with acenocoumarol, the risk of overanticoagulation when using CYP2C9 metabolised NSAIDs was modified by allelic variants of CYP2C9, especially CYP2C9*3. This was not observed with phenprocoumon. Possibly there were not enough patients included in this study for a firm conclusion.

Patients who have a variant CYP2C9 enzyme and use acenocoumarol are at greater risk of INR values above 4.9 when concomitant NSAIDs are used (60). Analysis of the variant groups for NSAID users shows that there is no difference within the wild-type subgroups, because these patients have the full capacity for eliminating drugs. An increase in the measured INRs is seen only in the subgroup of patients with CYP2C9 variants type *2 or *3 who also use NSAIDs. The capacity of the CYP2C9 variant polymorphisms to hydroxylate substrate drugs is diminished, and the administration of two substrate drugs may have pharmacokinetic effects on the elimination on one or both drugs.

Masche et al. investigated the effect of the co-administration of the NSAID lornoxicam on S- and R- phenprocoumon and found that it mainly alters the pharmacokinetics of S-phenprocoumon (61).

Conclusion

Knowing about the presence of both CYP2C9 and VKORC1 in the patient's genotype broadens our insight into the activity of the different coumarin anticoagulants in the individual patient contributing to a safer pharmacotherapy (62–66).

The effect of VKORC1 allelic variants is relatively similar for all three VKAs and explains 25% of the variance of the response to coumarin anticoagulant therapy. The effect of the CYP2C9*2 and *3 polymorphisms is most prominent for warfarin. For acenocoumarol, only CYP2C9*3 has an effect. For phenprocoumon, we observe a marginal effect of the CYP2C9 polymorphisms, which is probably limited to patients without a VKORC1 variant allele.

The combination of variant VKORC1 and CYP2C9 alleles explains a major part of the inter-individual differences in VKAs dosages (67). The combination of variant VKORC1 and CYP2C9 alleles increases the risk of major bleedings. The impact of the combination of the polymorphisms is the greatest in the initial weeks of starting coumarin anticoagulant therapy. Delayed stabilisation is associated with having a CYP2C9 polymorphism. The CYP4F2 genetic variant alters the required warfarin dose, data for acenocoumarol and phenprocoumon are lacking. Race-based differences in warfarin maintenance dose seems mainly dependent on the linked VKORC1 variants. Although speculative, one can expect the same pattern for acenocoumarol and phenprocoumon.

From a clinical perspective, phenprocoumon seems preferable for therapeutic anticoagulation in the absence of pharmacogenetic testing. Phenprocoumon therapy shows the least risk of delayed destabilisation compared to warfarin or acenocoumarol. The effects of CYP2C9 polymorphisms on the pharmacokinetics and anticoagulant response are least pronounced in the case of phenprocoumon. Patients on phenprocoumon have INR values more often in the therapeutic window and require less control than patients on acenocoumarol. The drug-drug pharmacokinetic interactions with NSAIDs are the least pronounced for phenprocoumon.

Pharmacogenetic testing may add to the safety of coumarin anticoagulant therapy. Pharmacoeconomic evaluations of pharmacogenetic testing suggest this is cost-effective for acenocoumarol and warfarin (68, 69).

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